UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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MAY - 6 1993

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Trifluralin (Compound 036352): Review of a 1-year dog study

Caswell No. 889	**DP Barcode:** D182358
MRID No. 424470-01	**EPA Case No.** 818802
EPA ID No. 036101	**Submission:** S424973

TO: Terri Stowe / Walter Waldrop, PM Team 71
Special Review and Registration Division (H7508C)

FROM: Whang Phang, Ph.D. 5/4/93
Pharmacologist
Tox. Br. II/HED (H7509C)

THROUGH: James Rowe, Ph.D. James N. Rowe 5/4/93
Section Head
and
Marcia van Gemert, Ph.D.
Branch Chief
Tox. Br. II/HED (H7509C)

The registrant, DowElanco, submitted a 1-year toxicity study in dogs with oral administration of Trifluralin (by capsule). This study has been reviewed; the data evaluation report is attached and the conclusion is as follows:

Adams, E.R., Bernhard, N.R., and Jordan, W.H. (1992) A chronic toxicity study of trifluralin (Compound 036352) administered orally to beagle dogs for 1 year. Unpublished study by Toxicology Research Laboratories, Lilly Research Laboratories. Study No. D07190. August 6,1992. Submitted to EPA by DowElanco. EPA MRID No. 424470-01.

Groups (Groups 00, 01, 02,& 03) of beagle dogs (4/sex/dose) orally received trifluralin by capsule at doses of 0, 0.75, 2.4, and 40 mg/kg, respectively, for a year.

The results showed that trifluralin at doses of 0.75 and 2.4 mg/kg produced minimal or no toxicity. <u>At 40 mg/kg, the test article produced the following compound-related effects</u>:

1. a decrease in the body weights of female dogs towards the

last 6 months of the study. The decrease was approximately 15% relative to the body weight of the controls,

2. a decrease in erythrocyte counts and hemoglobin in male and female dogs,

3. an increase in thrombocyte counts in male and female dogs,

4. an increase in methemoglobin in male and female dogs,

5. an increase in the cholesterol and triglyceride levels in males,

6. an increase in the absolute liver weights and the ratios of liver:body weight and liver:brain weight in males and females, and

7. a decrease in absolute heart weights and the ratio heart:brain weight.

Based upon the results of decrease in body weights, decrease in erythrocytes, increase in methemoglobin, increase in absolute and relative liver weights, and increase in cholesterol and triglyceride, the LOEL was 40 mg/kg; NOEL, 2.4 mg/kg.

This study for the most part meets the data requirements for a chronic non-rodent toxicity study (Guideline No. 83-1), and it is classified as **core minimum**.

The current RfD for trifluralin is 0.0075 mg/kg/day, which is based on the NOEL of 0.75 mg/kg derived from a previous 1-year toxicity study in dogs. The results of this study indicated that the NOEL, 2.4 mg/kg, is approximately 3 times higher than the previous NOEL (0.75 mg/kg), and the current data indicate a need to request the RfD Committee to consider the findings of the current study in regards to the RfD for trifluralin.

In your Data Package Record Bean Sheet for this task, you also requested this reviewer to "identify all applicable data requirements and note those for which adequate data have not been submitted to the Agency". In January of 1992, I responded to you about the toxicology data requirements on Trifluralin in regards to a dermal absorption study data waiver request by DowElanco (Memorandum of W. Phang to T. Stowe/W. Waldrop, Jan 15, 1992). The toxicology data requirements have not changed, and the Agency still need a dermal absorption study on trifluralin (see Appendix A).

CC: Dr.George Ghali
RfD Committee, SACB/HED (H7509C)

Appendix A.

CASWELL FILE

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Trifluralin: Evaluation of a data waiver request

Caswell No. 889 HED Project No. 2-0280
EPA ID No. 036101 Submission No. S405966

TO: T. Stowe / W. Waldrop, PM Team 71
Special Review and Re-registration Division (H7508W)

FROM: Whang Phang, Ph.D. 1/13/92
Pharmacologist
Tox. Branch II / HED (H7509C)

THROUGH: James Rowe, Ph.D. 1/13/92
Section Head, Section III
and
Marcia van Gemert, Ph.D. 1/13/92
Branch Chief
Tox. Branch II / HED (H7509C)

Introduction

In 1991, Tox. Branch II was requested to evaluate a dermal absorption study on trifluralin in rhesus monkeys. The study was reviewed by R. Zendzian, Ph.D. and found to have significant deficiencies. It was concluded that the study is unacceptable, and the data can not be used for risk assessment purposes. The registrant, DowElanco, responded to the review of the study and requested to meet with the Agency to discuss the study. In addition, SRRD also requested Tox. Branch II to "identify all applicable data requirements and to note those for which adequate data have not been submitted to the Agency".

Discussion

The Toxicology Branch II is looking forward to meeting with the representatives of DowElanco to listen to any reasons for waiving the data requirement for a dermal absorption study.

This reviewer has examined the available toxicology data file on trifluralin and found essentially all applicable data requirements

stated on the Registrant Standard for Trifluralin (April 1987) are satisfied except a dermal absorption study. The following is a summary of all the required toxicology studies and the Core classification:

Study Type	Core Class.	Comments
Acute Studies		
Acute oral tox.-rat	Guideline	LD_{50} >5000 mg/kg Tox. Cat.IV
Acute dermal tox.-rabbit	Guideline	LD_{50}>2 g/kg Tox. Cat.III
Acute Inhalation-rat	Guideline	LC_{50}>4660 mg/m^3 Tox. Cat.IV
Eye irritation-rabbit	Guideline	Conjunctivitis (cleared by day 4) Tox. Cat. III
Primary dermal Irrit.-rabbit	Guideline	not a skin irritant Tox. Cat. IV
Dermal sensitization-guinea pig	Guideline	produced skin sensitization
Subacute Studies		
90-day feeding-rat	Minimum	NOEL = 50 ppm
6-month feeding-dog	Supplementary*	NOEL < 400 ppm (LDT)
90-day dermal-rat	Minimum	NOEL = 200 mg/kg
Long-term studies		
1-year feeding-dog	Guideline	NOEL = 30 ppm
Chronic feeding/Onco. -rat	Guideline	NOEL = 200 ppm Significant increase in tumor incidence was not reported. However, in a study conducted on Fischer 344 rats by Eli Lilly, an increase in tumor incidence of the renal pelvis and urinary bladder was seen. The Peer Review Committee on Carcinogenicity of HED has classified trifluralin as a Category C carcinogen.
Onco. study-mouse	Minimum	NOEL = 50 ppm no carcinogenic potential was found.

Developmental toxicity studies

Develop. tox.-rat	Minimum	NOEL for develop. tox.= 475 mg/kg
Develop. tox-rabbit	Minimum	NOEL for develop. tox.= 225 mg/kg

Reproduction studies

2-generation reprod.-rat	Minimum	NOEL for reproductive parameters=0.2% (2000 ppm)

Mutagenicity studies

Ames	Acceptable	Negative
Sister chromatid exchange (Chinese Hamster BM)	Acceptable	Negative
Dominant lethal-mouse	Acceptable	Negative
Dominant lethal-rat	Acceptable	Negative
Micronucleus assay-mouse	Acceptable	Negative

Metabolism studies

The available data on the metabolism of trifluralin are considered to be sufficient for understanding the metabolic fate of this chemical.

Dermal penetration study

An acceptable dermal penetration study conducted according to the Agency's guidelines is required.

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*: An acceptable chronic feeding study on dog is available, and the requirement on a 90-day dog study may be waived.